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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A MONOAMINE NEUROTRANSMITTER RE-UPTAKE INHIBITOR AND A DOPAMINE AGONIST

(57) Abstract: The invention relates to a pharmaceutical composition comprising a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

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Pharmaceutical Composition Comprising a monoamine neurotransmitter re-uptake inhibitor and a dopamine agonist

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to a combination of a monoamine neurotransmitter re-uptake inhibitor and a dopamine agonist, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.

2. BACKGROUND INFORMATION

Alzheimer's disease is a poorly understood neurodegenerative condition mainly affecting the elderly but also younger people who are generally genetically pre-dispositioned to it.

One postulated method of treatment comprises the administration of dopamine agonists which act on the cholinergic system.

However this method suffers from the disadvantages that these compounds induce a range of side-effects including diarrhoea, salivation and nausea.

The International patent application WO 97/30997 discloses tropane derivatives, which are monoamine neurotransmitter re-uptake inhibitor. Similar compounds are known from the International patent application WO 93/09814.

However, there is no hint to combine these compounds with a dopamine agonist.

The present invention provides a new and surprisingly effective combination of a dopamine agonist and a monoamine neurotransmitter re-uptake inhibitor for separate, sequential or simultaneous administration.

Surprisingly, an unexpectedly beneficial therapeutic effect can be observed if dopaminergic agonists are used in combination with a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety:

BRIEF SUMMARY OF THE INVENTION

Accordingly, the invention relates to a pharmaceutical composition comprising a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

The present invention provides a greater than expected improvement in the condition of subjects suffering from a neurodegenerative disorder with an associated cognitive deficit, such as Alzheimer's Disease, or from a cognitive deficit which may arise from a normal process such as aging or from an abnormal process such as injury, than would be expected from administration of the active ingredients alone. Further, the combination allow a lower overall dose of each of the active ingredients to be administered thus reducing side effects and decreasing any reduction in the effectiveness of each of the active ingredients over time.

There is also provided a kit of parts comprising at least two separate unit dosage forms (A) and (B):

(A) one of which comprises a composition a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and optionally a pharmaceutically acceptable carrier;

(B) one of which comprises a composition containing one or more dopamine agonists or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and optionally a pharmaceutically acceptable carrier,

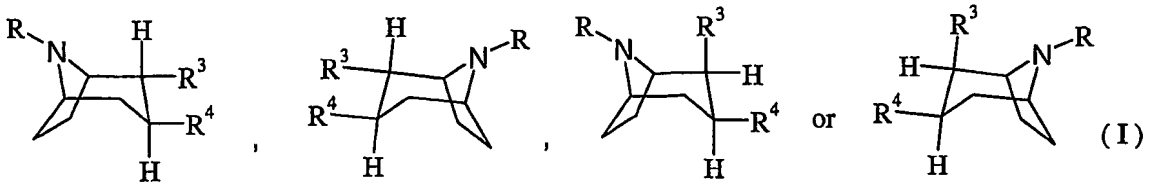
for simultaneous, sequential or separate administration.

There is also provided the use of a combination of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2) in a combined form, or separately or separately and sequentially, wherein the sequential administration is close in time or remote in time, for the manufacture of a medicamentation for the prevention or treatment of a disease or a disorder, which is responsive to the inhibition of monoamine neurotransmitter re-uptake and or to dopamine agonism.

There is also disclosed a method of prevention or treatment of a disease or disorder, which disease or disorder is responsive to the inhibition of monoamine neurotransmitter re-uptake, which method comprises administration of effective amounts of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2) to a patient in need thereof in a combined form, or separately or separately and sequentially wherein the sequential administration is close in time or remote in time.

DETAILED DESCRIPTION OF THE INVENTION

As a rule the monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety are compounds of the general formula (I)



(I)

or a pharmaceutical acceptable addition salt thereof or the N-oxide thereof, wherein

R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl or 2-hydroxyethyl;

R^3 is CH_2-X-R',

wherein X is O, S, or NR"; wherein

R" is hydrogen or alkyl; and

R' is alkyl, alkenyl,alkynyl, cycloalkyl,cycloalkylalkyl, or-CO-alkyl;

heteroaryl which may be substituted one or more times with

alkyl, cycloalkyl, or cycloalkylalkyl;

phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl,alkynyl, amino, nitro, and heteroaryl;

phenylphenyl;

pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;

thienyl which may be substituted one or more times with substituents selected from the group consisting ofhalogen, CF_3, CN, alkoxy, alkyl, alkenyl,alkynyl, amino, nitro, and heteroaryl ; or

benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; or

$(CH_2)_nCO_2R^{11}$, COR^{11}, or CH_2R^{12} , wherein

R^{11} is alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; phenylphenyl ; pyridyl which may be substituted one or more times with substituents selected from

the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; o thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; or benzyl;

n is 0 or 1; and

R^{12} is O-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
O-CO-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or
CH=NOR' ; wherein R' is o hydrogen; o alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl ; all of which may be substituted with-COOH; -COO-alkyl; -COO-cycloalkyl ; or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro;

R^4 is phenyl, 3,4-methylenedioxyphenyl, benzyl, naphthyl, or heteroaryl all of which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a special embodiment of the compound of general formula I, R^3 is 1,2,4-oxadiazol-3-yl which may by substituted in the 5 position with alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted one or more times with substituents selected from the group consisting ofhalogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; phenylphenyl; or benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or 1,2,4-oxadiazol-5-yl which may by substituted in the 3 position with alkyl, cycloalkyl, or cycloalkylalkyl; phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3,

CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; phenylphenyl; benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro and heteroaryl; or thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl,alkynyl, amino, nitro and heteroaryl.

In a further special embodiment of the compound of general formula (I), R^3 is .CH_2-X-R', wherein X is O, S, or NR"; wherein R" is hydrogen or alkyl ; and
R' is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, or-CO-alkyl.

In a still further embodiment of the compound of general formula (I), R^3 is CH=NOR'; wherein R' is hydrogen; alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl ; all of which may be substituted with -COOH; -COO-alkyl; -COO-cycloalkyl; or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro.

In a further special embodiment of the compound of general formula (I), R^4 is phenyl, which is substituted once or twice with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

In a more special embodiment, R^4 is phenyl substituted once or twice with chlorine.

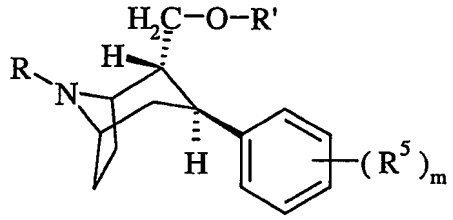
In a further special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a (1 R, 2R, 3S) -2, 3-disubstituted tropane derivative of formula I.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R^3 is-CH_2-X-R', wherein X is O or S, and R' is methyl, ethyl, propyl, or cyclopropylmethyl; -CH=NOR'; wherein R' is hydrogen or alkyl, or 1,2,4-oxadiazol-5-yl which may by substituted in the 3 position with alkyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I wherein R is hydrogen, methyl, ethyl or propyl.

In a still further embodiment, the tropane derivative having dopamine reuptake inhibitory activity is a compound of general formula I whereinR^4 is 3,4-dichlorophenyl.

Preferably those monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety are compounds of formula (I1)



(I 1)

wherein

R represents a hydrogen atom or a C_{1-6} alkyl group, preferably a hydrogen atom, a methyl or an ethyl group;

R^5 each independently represents a halogen atom or a CF_3 or cyano group, preferably a fluorine, chlorine or bromine atom;

R' represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group, preferably a methyl, ethyl or n-propyl group; and

m is 0 or an integer from 1 to 3, preferably 1 or 2;

or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1).

As used herein, the expression"C_{1-6} alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

The expression"C_{3-6} cycloalkyl" as used herein includes cyclic propyl, butyl, pentyl and hexyl groups such as cyclopropyl and cyclohexyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

The term "physiologically functional derivative" as used herein includes derivatives obtained from the compound of formula (I) under physiological conditions, these are for example N-oxides, which are formed under oxidative conditions.

The term "pharmaceutically acceptable acid addition salt" as used herein includes those salts which are selected from among the acid addition salts formed with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid, the salts obtained from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and acetic acid being particularly preferred. The salts of citric acid are of particular significance.

In a special embodiment, the tropane derivative having dopamine reuptake inhibitor activity is a compound of the general formula (I) selected from:

(1 R, 2R, 3S)-2-(3-Cyclopropyl-1, 2, 4-oxadiazol-5-yl)-3- (4-fluorophenyl) tropane;
(1R,2R,3S)-2-(3-Phenyl-1, 2,4-oxadiazol-5-yl)-3- (4-fluorophenyi) tropane;
(1R,2R,3S)-2-(3-Phenyl-1, 2,4-oxadiazol-5-yl)-3- (4-methylphenyl)-tropane;
(1 R, 2R, 3S)-2-(3-Benyl-1, 2, 4-oxadiazol-5-yl)-3- (4-fluorophenyl) tropane;
(1 R, 2R, 3S)-2- (3- (4-Phenyl-phenyl)-1, 2, 4-oxadiazol-5-yl)-3- (4-fluorophenyl) tropane;
(1 R, 2R, 3S)-2-(3-Phenyl-1, 2, 4-oxadiazol-5-yl)-3-(2-naphthyl) tropane;
(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl)-tropane-2-O-methyl-aldoxime;

(1 R, 2R, 3S)-3-(3,4-Dichlorophenyl)tropane-2-O-benzyl-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-O-ethoxycarbonylmethyl-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-O-methoxycarbonylmethyl-aldoxime;

(1 R, 2R, 3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1-ethoxycarbonyl-1,1-dimethyl-methyl)-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-O-carboxymethyl-2-aldoxime;

(1 R, 2R,3S)-N-Normethyl-3- (3, 4-dichlorophenyl) tropane-2-O-methyl-aldoxime;

(1 R, 2R,3S)-N-Normethyl-3- (3, 4-dichlorophenyl) tropane-2-O-benzyl-aldoxime;

(1 R, 2R,3S)-3- (4-Methylphenyl) tropane-2-O-methyl-aldoxime;

(1 R, 2R,3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(1,1-dimethylethyl)-aldoxime;

(1 R, 2R,3S)-3- (4-Chlorophenyl) tropane-2-O-aldoxime;

(1 R, 2R,3S)-3- (4-Chlorophenyl) tropane-2-O-methylaldoxime hydrochloride;

(1 R, 2R, 3S)-3-(4-Chlorophenyl)tropane-2-O-methoxycarbonylmethyl-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-O- (2-propynyl)-aldoxime;

(1 R, 2R, 3S)-3-(3,4-Dichlorophenyl)tropane-2-O-(2-methylpropyl)-aldoxime;

(1 R, 2R, 3S)-3-(3,4-Dichlorophenyl)tropane-2-O-cyclopropylmethyl-aldoxime;

(1 R, 2R,3S)-3- (3, 4-Dichlorophenyl) tropane-2-O-ethyl-aldoxime;

(1 R, 2R,3S)-2-Methoxymethyl-3- (3, 4-dichlorophenyl)-tropane;

(1R,2R,3S)-2-Isopropoxymethyl-3-(3,4-dichlorophenyl)-tropane;

(1 R, 2R,3S)-2-Ethoxymethyl-3- (3, 4-dichlorophenyl)-tropane;

(1 R, 2R,3S)-2-Ethoxymethyl-3- (3, 4-dichlorophenyl)-nortropane;

(1 R, 2R, 3S)-2-Cyclopropylmethyloxymethyl-3- (3, 4-dichlorophenyl)-tropane;

(1 R, 2R,3S)-2-Methoxymethyl-3- (4-chlorophenyl)-tropane;

(1 R, 2R,3S)-N-Normethyl-2-methoxymethyl-3- (4-chlorophenyl)-tropane;

(1R,2R,3S)-2-Ethoxymethyl-3-(4-chlorophenyl)-tropane;

(1 R, 2R,3S)-N-Normethyl-2-methoxymethyl-3- (3, 4-dichlorophenyl)-tropane;

(1R,2R,3S)-N-Normethyl-2-ethoxymethyl-3-(3,4-dichlorophenyl)-tropane;

(1 R, 2R,3S)-N-Normethyl-2-ethoxymethyl-3- (4-chlorophenyl)-tropane;

(1 R, 2R,3S)-N-Normethyl-2-cyclopropylmethyloxymethyl-3- (4-chlorophenyl)-tropane;

(1 R, 2R, 3S)-2-Cyclopropylmethyloxymethyl-3- (4-chlorophenyl)-tropane;

(1 R, 2R, 3S)-2-Ethylthiomethyl-3-(3,4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-2-Hydroxymethyl-3-(4-fluorophenyl) tropane;

(1 R, 2R, 3S)-2-Hydroxymethyl-3-(3,4-dichlorophenyl) tropane;

(1 R, 2R, 3S)-N-Normethyl-N-(tert-butoxycarbonyl)-2-hydroxymethyl-3-(3,4-dichlorophenyl) tropane;

(1 R, 2R, 3S)-2-Hydroxymethyl-3-(4-chlorophenyl) tropane;

(1 R, 2R,3S)-2- (3- (2-Furanyl)-1, 2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-2-(3-(3-Pyridyl)-1, 2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;

(1R,2R,3S)-N-Normethyl-N-allyl-2-(3-(4-pyridyl)-1, 2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-N-Normethyl-N-ethyl-2-(3-(4-pyridyl)-1,2,4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;

(1 R,2R, 3S)-N-Normethyl-N- (2-hydroxyethyl)-2- (3- (4-pyridyl)-1, 2, 4-oxadiazol-5-yl)-3- (3,4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-N-Normethyl-2- (3- (4-pyridyl)-1, 2, 4-oxadiazol-5-yl)-3- (3, 4-dichlorophenyl)- tropane;

(1 R, 2R, 3S)-N-Normethyl-N-allyl-2- (3- (3-pyridyl)-1, 2, 4-oxadiazol-5-yl)-3-(3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-N-Normethyl-N-allyl-2-(3-(2-pyridyl)-1, 2, 4-oxadiazol-5-yl)-3- (3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-2- (3- (2-Thienyl)-1, 2, 4-oxadiazol-5-yl)-3- (4-chlorophenyl)-tropane;

(1 R, 2R, 3S)-2-(3-(2-Thienyl)-1, 2, 4-oxadiazol-5-yl)-3- (3, 4-dichlorophenyl)-tropane;

(1R,2R,3S)-2-(3-(4-Pyridyl)-1, 2,4-oxadiazol-5-yl)-3- (3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-2- (3- (2-Pyridyl)-1, 2, 4-oxadiazol-5-yl)-3- (3, 4-dichlorophenyl)-tropane;

(1 R, 2R, 3S)-2- (3- (4-Pyridyl)-1, 2, 4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;

(1 R, 2R, 3S)-2- (3- (3-Pyridyl)-1, 2, 4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;

(1R,2R,3S)-2-(3-2-Pyridyl)-1, 2, 4-oxadiazol-5-yl)-3-(4-chlorophenyl)-tropane;

(1 R, 2R,3S)-2- (3-Phenyl-1, 2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;

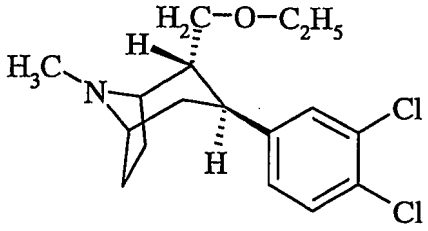
(1 R, 2R,3S)-2- (3-Phenyl-1, 2,4-oxadiazol-5-yl)-3- (4-methylphenyl)-tropane;

(1 R, 2R,3S)-2- (3-Benzyl-1, 2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;

(1 R, 2R,3S)-2- (3- (4-Phenylphenyl)-1, 2, 4-oxadiazol-5-yl)-3-(4-fluorophenyl)-tropane;

(1 R, 2R,3S)-2- (3-Phenyl-1, 2, 4-oxadiazol-5-yl)-3-(2-naphthyl)-tropane;
(1 R, 2R,3S)-2- (4-Chlorophenoxy-methyl)-3- (4-fluorophenyl)-tropane;
(1 R, 2R,3S)-2- (4-Chlorophenoxy-methyl)-3- (4-fluorophenyl)-tropane;
(1 R, 2R, 3S)-2-(4-Chlorophenoxy-methyl)-3-(3,4-dichlorophenyl)-tropane;
(1R, 2R,3S)-2- (4-Chlorophenoxy-methyl)-3- (4-methylphenyl)-tropane;
(1R, 2R, 3S)-2-(4-Benzoyloxy-methyl)-3-(4-fluorophenyl)-tropane;
(1 R, 2R, 3S)-2-Carbomethoxy-3-(2-naphthyl)-tropane;
(1 R, 2R, 3S)-2-Carbomethoxy-3-(3,4-dichlorophenyl)-tropane;
(1 R, 2R, 3S)-2-Carbomethoxy-3-benzyl-tropane;
(1 R, 2R, 3S)-2-Carbomethoxy-3- (4-chlorophenyl)-tropane;
(1 R, 2R, 3S)-2-Carbomethoxy-3- (4-methylphenyl)-tropane;
(1 R, 2R,3S)-2-Carbomethoxy-3- (1-naphthyl)-tropane;
(1 R, 2R,3S)-2-Carbomethoxy-3- (4-phenylphenyl)-tropane;
(1 R, 2R,3S)-2-Carbomethoxy-3- (4-t-butyl-phenyl)-tropane;
(1 R, 2R, 3S)-2-(4-Fluoro-benzoyl)-3-(4-fluorophenyl)-tropane; or a pharmaceutically acceptable addition salt thereof.

Most preferred is the compound of formula (IA)



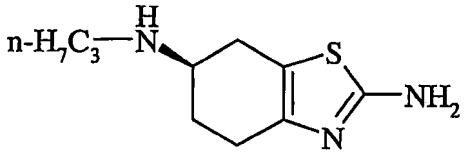
(IA)

or a pharmaceutically acceptable salt thereof, in particular the citrate thereof.

Dopamine agonists which may be used include any which are known to the skilled person and those which will become available in the future. Examples are .
amisulpride, amisulpride, bromocriptine, buspirone, cabergoline, docarpamine, dopexamine ,etilevodopa, fenoldopam, ibopamine, lisuride, nolomirole, pergolide, piripedil, pramipexole, quinagolide, quinelorane, ropinirole, rotigotine, roxindole, sibenadet, sumanirole, talipexole and terguride.

Preferred is a combination of the compound of formula (IA) with a dopamine agonists selected from the group consisting of pramipexole (2), its dihydrochloride (3) and its dihydrobromide (4), ropinirole (5), rotigotine (6), roxindole (7), sibenadet (8) and talipexole (9).

Most preferred is a combination of the compound of formula (IA) with pramipexole, which is (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole (1) of formula



the dihydrochloride thereof or the dihydrochloride monohydrate thereof.
Particularly preferred are combinations selected from the group consisting of compound combinations (1) with (2), (1) with (3), (1) with (4), (1) with (5), (1) with (6), (1) with (7), (1) with (8) and (1) with (9).

The pharmaceutical compositions of the present invention are suitable for oral, intravenous, intravascular, intraperitoneal, subcutaneous, intramuscular, inhalativ, topical, patch or suppository administration.

The pharmaceutical compositions of the present invention are preferably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e. g. conventional tabletting ingredients such as corn starch, cellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, lactose, sucrose, sorbitol, talc, silicon dioxide, polyethylene glycol, stearic acid, magnesium stearate and dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and

other pharmaceutical diluents, e. g. water, to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these pre-formulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

This solid pre-formulation composition is then subdivided into unit dosage forms of the type described above containing from 0.01 to 10,000 mg, in particular 0.05 to about 500 mg, most preferably 0.75 to 250 mg of each active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of each active ingredient.

Most preferably, 0.025 to 1.5 mg, in particular 0.044, 0.088, 0.18, 0.35, 0.7, or 1.1 mg of Pramipexole are together with 0.05 to 1.5 mg, in particular 0.06, 0.125, 0.25, 0.5, or 1.0 mg Of the compound of formula IA are administered :

The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably

flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

For preparing suppositories, a low melting was, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) or fluorohydrocarbon (HFC) for example dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2-tetrafluoroethan (HFC-134(a)), or 1,1,1,2,3,3,3-heptafluoroprpane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin and/or a co-solvent such as ethanol. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

In a preferred embodiment of the inventive kit of parts pramipexole is administered via a transdermal patch as disclosed for example by EP 0 428 038 Case 3/0327 and the compound of formula (IA) is administered orally.

For the treatment of a Parkinson disease or depression, a suitable dosage level is about 0.01 to 1.0 mg/kg per day, preferably about 0.02 to 0.5 mg/kg per day, and especially about 0.05 to 0.2 mg/kg of body weight per day of each active ingredient. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

Most preferably the composition of the invention will be used for the treatment or prevention of one or more of the following neurodegenerative conditions:

Parkinson´s disease, pseudodementia, dementia, including dementia of Alzheimer Type, Alzheimer's disease, presenile dementia, senile dementia, Lewy-Body-dementia, Down syndrome, fronto temporal dementia, HIV related dementia, Pick's disease, multi-infarct dementia, memory deficits, attention deficits, cognitive dysfunction, memory dysfunction, mild cognitive impairment, age associated memory impairment, ageing-associated cognitive decline, age-related cognitive decline, ALS and multiple system atrophy.

Preferably the weight ratio of (1) to (2) ranges from 50 : 1 to 1 : 300, in particular from 1 : 1 to 1 : 200 most preferably from 1 : 2 to 1 : 50.

The Examples that follow serve to illustrate some formulations according to the invention. They are intended solely as possible procedures described by way of example, without restricting the invention to their content.

Example 1

A pharmaceutical composition is prepared by combining pramipexole in either its racemic or entantiomeric form with the compound of formula (IA) in a pharmaceutically acceptable carrier. The composition contains respective amounts of pramipexole and formula (IA) to deliver on a daily basis between about 0.05 mg to about 1.5 mg pramipexole and between about 0.1 mg to about 2 mg of formula (IA) per kilogram of patient body weight (for example, 6 mg to 120 mg formula (IA) for a person weighing 60 kg). The composition is administered to a patient for the treatment of Parkinsonism, Alzheimer disease or depression.

Example 2

A first pharmaceutical composition is prepared by combining pramipexole in either its racemic or enantiomeric form in a pharmaceutically acceptable carrier such that it can deliver between about 0.05 mg to about 1.5 mg pramipexole on a daily basis.

A second pharmaceutical composition is prepared by combining formula (IA) in a pharmaceutically acceptable carrier such that it can deliver between about 0.05 mg to about 2 mg of formula (IA) per kilogram of patient body weight on a daily basis. The first composition is administered to a patient suffering from Parkinsonism, Alzheimer disease or depression once, twice, three times, four times or six times daily such that the daily dosage is between about 0.1 to about 10 mg. The second composition is administered to the same patient at the same time as the administration of the first composition or any time within 24 hours of the administration of the first composition once, twice, three times, four times or six times daily such that the daily dosage is between about 0.1 mg to about 2 mg of formula (IA) per kilogram of patient body weight.

Alternatively, the second composition could first be administered, followed by the

administration of the first composition as disclosed at the same time, or within 24 hours thereof.

Example 3 Composition of (IA) / Pramipexole film-coated tablet 0.25 mg / 0.18 mg

Core

Constituents	**mg/tablet**
(IA) citrate	0.396
Pramipexole dihydrochloride	0.24
Lactose monohydrate (200 mesh)	101.130
Microcrystalline cellulose (grade PH 101)	69.000
Corn starch	6.300
Purified water (q.s.)*	
Sodiumstarchglycolate	3.600
Colloidal silicon dioxide	0.900
Magnesium stearate	1.800

Coating

Constituents	**mg/ tablet**
Hydroxyproylmethylcellulose 2910	2.750
Polyethylene Glycol 400	0.325
Titanium dioxide	1.000
Talc	0.925
Purified water	(q.s.)*

* *does not appear in final product*

Total weight film coated tablet	**185.000**

Example 4 – Composition of (IA) / Pramipexole capsules 0.15 mg / 0.6 mg

Granules

Constituents	**mg/capsule**
(IA) citrate	0.238
Pramipexole dihydrochloride	0.801
Microcrystalline cellulose	71.592
Dibasic calcium phosphate, anhydrous	71.494
Hypromellose	2.750
Carboxymethylcellulose sodium, crosslinked	2.000
Purified water (q.s.)*	
Colloidal silicon dioxide	0.375
Magnesium stearate	0.750

* *does not appear in final product*

Capsules

Constituents	**mg/ capsule**
Granules	150.000
Hard-gelatin capsule (size 2)	61.000
Total weight capsule	**211.000**

Example 5 – Composition of (IA) / Pramipexole bilayer tablets 0.25 mg / 4 mg

Bilayer tablet

Constituents	**mg/tablet**
1st tablet layer	

(IA) citrate	0.396
Lactose monohydrate (200 mesh)	70.104
Microcrystalline cellulose (grade PH 101)	42.000
Corn starch	4.200
Purified water	(q.s.)*
Sodiumstarchglycolate	2.400
Magnesium stearate	0.900

2nd tablet layer	**mg/ tablet**
Pramipexole dihydrochloride	5.342
Sorbitol, powder	120.308
Microcrystalline Cellulose	14.000
Crospovidone	2.800
Magnesium stearate	1.750

* does not appear in final product

Total weight bilayer tablet	**260.000**

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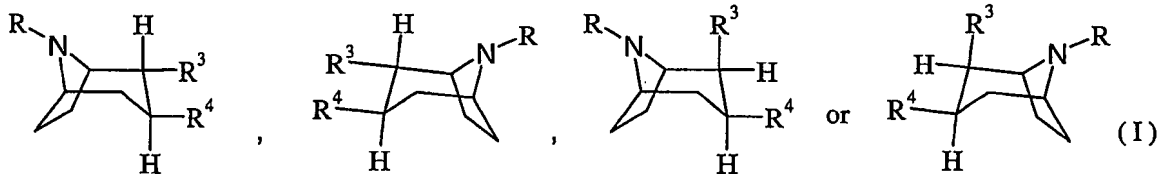
CLAIMS:

1. A pharmaceutical composition comprising a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1), and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

2. A pharmaceutical composition according to claim 1 wherein said monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety is a compound of formula



(I)

or a pharmaceutical acceptable addition salt thereof or the N-oxide thereof, wherein
R is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl or 2-hydroxyethyl;
R^3 is

CH_2-X-R', wherein

X is O, S, or NR"; wherein

R" is hydrogen or alkyl; and

R' is alkyl, alkenyl,alkynyl, cycloalkyl,cycloalkylalkyl, or-CO-alkyl;

heteroaryl which may be substituted one or more times with

alkyl, cycloalkyl, or cycloalkylalkyl;

phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl,alkynyl, amino, nitro, and heteroaryl;

phenylphenyl;

pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;

thienyl which may be substituted one or more times with substituents selected from the group consisting ofhalogen, CF_3, CN, alkoxy, alkyl, alkenyl,alkynyl, amino, nitro, and heteroaryl ; or

benzyl which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ; or

$(CH_2)_nCO_2R^{11}$, COR^{11}, or CH_2R^{12}

wherein R^{11} is

alkyl, cycloalkyl, or cycloalkylalkyl;

phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl ;

phenylphenyl;

pyridyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl;

thienyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

benzyl;

n is 0 or 1; and

R^{12} is

O-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

O-CO-phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen, CF_3, CN, alkoxy, alkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl; or

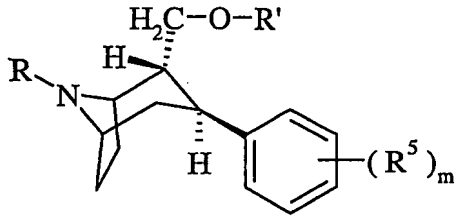
CH=NOR' ; wherein R' is o hydrogen; o alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl or aryl ; all of which may be substituted with-COOH; -COO-alkyl; -COO-cycloalkyl ; or phenyl which may be substituted one or more times with substituents selected from the group consisting of halogen,CF_3, CN, alkyl, cycloalkyl, alkoxy, cycloalkoxy, alkenyl, alkynyl, amino, and nitro;

R^4 is

3,4-methylenedioxyphenyl or

phenyl, benzyl, naphthyl or heteroaryl all of which may be substituted one or more times with substituents selected from the group consisting of halogen,CF3, CN, alkoxy, cycloalkoxy, alkyl, cycloalkyl, alkenyl, alkynyl, amino, nitro, and heteroaryl.

3. A pharmaceutical composition according to claim 1 or 2 wherein said monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety is a compound of formula (I1)



(I1)

wherein

R represents a hydrogen atom or a C_{1-6} alkyl group;

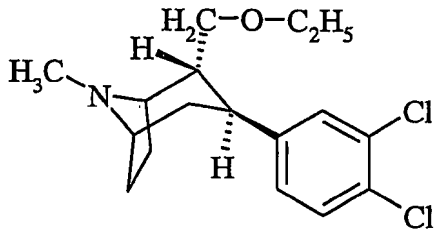
R^5 represents a halogen atom or a CF_3 or cyano group;

R' represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group; and

m is 0 or an integer from 1 to 3;

or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1).

4. A pharmaceutical composition according to any one of claims 1 to 3 consisting essentially of the compound of formula (IA)



(IA)

or a pharmaceutically acceptable salt thereof, (1) and one dopamine agonist selected from the group consisting of amisulpride, amisulpride, bromocriptine, buspirone, cabergoline, docarpamine, dopexamine ,etilevodopa, fenoldopam, ibopamine, nolomirole, pergolide, pramipexole, quinagolide, quinelorane, ropinirole, rotigotine, roxindole, sibenadet, talipexole and tergurideor a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2), and a pharmaceutically acceptable carrier or excipient.

5. A pharmaceutical formulation according to any of claims 1 to 4 which is suitable for oral, intra venous, intravascular, intraperitoneal, subcutaneous, intramuscular or topical or patch or suppository administration.

6. A pharmaceutical formulation according to any of claims 1 to 5 wherein the weight ratio of (1) to (2) ranges from 50:1 to 1 : 300.

7. A pharmaceutical formulation according to any of claims 1 to 6 wherein a single application dose contains 1 to 10,000 milligrams of the combined active ingredients (1) and (2).

8. A pharmaceutical formulation according to any of claims 1 to 7 wherein the pharmaceutically acceptable carrier or excipient is selected from the group consisting of corn starch, cellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, lactose, sucrose, sorbitol, talc, silicon dioxide, polyethylene glycol, stearic acid, magnesium stearate and dicalcium phosphate.

9. A method for the prevention or treatment of a disease or disorder, which disease or disorder is responsive to the inhibition of monoamine neurotransmitter re-uptake, which method comprises administration of effective amounts of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a

tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2) to a patient in need thereof in a combined form, or separately or separately and sequentially wherein the sequential administration is close in time or remote in time.

10. A method according to claim 9, wherein said disease or disorder is selected from the group consisting of, Parkinsonism, depression, obesity, narcolepsy, drug addiction or misuse, including cocaine abuse, attention-deficit hyperactivity disorders, Gilles de la Tourettes disease, any dementia presented below, pseudodementia, dementia, including dementia of Alzheimer Type, Alzheimer's disease, presenile dementia, senile dementia, Lewy-Body-dementia, Down syndrome, fronto temporal dementia, HIV related dementia, Pick's disease, multi-infarct dementia, memory deficits, attention deficits, cognitive dysfunction, memory dysfunction, mild cognitive impairment, age associated memory impairment, ageing-associated cognitive decline, age-related cognitive decline and multiple system atrophy.

11. A method according to claim 10 wherein the disease or disorder is dementia of Alzheimer Type.

12. Use of a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (1) and at least one dopamine agonist or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (2) in a combined form, or separately or separately and sequentially, wherein the sequential administration is close in time or remote in time, for the manufacture of a medicamentation for the prevention or treatment of a disease or a disorder, which is responsive to the inhibition of monoamine neurotransmitter re-uptake and or to dopamine agonism.

13. Use according to claim 12 for the manufacture of a medicamentation for the prevention or treatment of a disease or disorder, which is selected from the group consisting of pseudodementia, dementia, including dementia of Alzheimer Type, Alzheimer's disease, presenile dementia, senile dementia, Lewy-Body-dementia, Down

syndrome, fronto temporal dementia, HIV related dementia, Pick's disease, multi-infarct dementia, memory deficits, attention deficits, cognitive dysfunction, memory dysfunction, mild cognitive impairment, age associated memory impairment, ageing-associated cognitive decline, age-related cognitive decline and multiple system atrophy.

14. A pharmaceutical kit comprising at least two separate unit dosage forms (A) and (B):

(A) one of which comprises a composition a monoamine neurotransmitter re-uptake inhibitor comprising a 2,3-disubstituted tropane moiety, or a tautomer, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (**1**), and optionally a pharmaceutically acceptable carrier;

(B) one of which comprises a composition containing one or more dopamine agonists or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof (**2**), and optionally a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/000166

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/46 A61K31/428 A61P25/28 A61P25/30 A61P25/16 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2005	24/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ansaldo, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/000166

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 01/62249 A (MARSHALL ROBERT C ; VONVOIGTLANDER PHILIP F (US); UPJOHN CO (US); WONG) 30 August 2001 (2001-08-30) abstract	1-13

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International Application No
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